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Abstract: Describes the conduct and result of a double-blind trial comparing oral intake of boron per day in the treatment of arthritis. Materials and methods used in the study; Comparison of treatment arms; Other factors possibly affecting the outcome of variables; Possible side effects of boron.

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BORON AND ARTHRITIS: THE RESULTS OF A DOUBLE-BLIND PILOT STUDY

This report describes the conduct and results of a double-blind trial comparing oral intake of 6 mg of boron per day to placedo the treatment of arthritis. The results indicate that boron may well be beneficial. Of the 10 patients on boron, five improved and five did not, but only one of the 10 patients on the placebo improved. This was essentially a pilot trial which showed that a small quantity of boron would greatly relieve severe osteo-arthritis. Of those starting the trial, 50% using boron improved as compared with 10% on placebo; or if we consider those who completed the trial, 71% improved while using boron. There were no side-effects and these were sought. The indication is that boron (as sodium tetraborate decahydrate) are safe and beneficial in the treatment of osteo-arthritis and that further research is required.

Keywords: arthritis, osteo-arthritis, boron.

INTRODUCTION

Boron has long been known to be essential for plants [1]. While scientific literature does not appear to contain evidence of its being essential for humans, many possible functions for boron in the

human body have been discussed [2]. The reported daily intake of boron by adults varies between 03 mg and 41 ma, depending on the geography. The content in foods also varies considerably; the highest value (25000 Mu g/100 g) being reported for honey [2].

Boric acid has been used medically for over 200 years as a sedative, spasmolytic, diuretic and as an external antiseptic. However, in recent years it has come somewhat into disrepute because of its toxicity (boron is currently listed in Schedule 4 of the Victorian Poisons Act and its sale is prohibited) and relative ineffectiveness. The lethal dose for infants is between 0.8 g and 3 g orally and for adults between 12 g and 30 g. In Germany, boric acid complexes in combination with calcium have been patented for therapeutic use as disinfectants and as anti-inflammatory drugs [3]. Boric acid is also used as a buffer in other pharmaceutical preparations.

Boron has been used in the treatment of arthritis for over 15 years now. During this time there has been no other proper scientific study of its efficacy in humans, although there was at least one unconfirmed report of its having worked for rats [4]. Hence the need for this (pilot) study.

MATERIALS AND METHODS

Twenty patients presenting with radiographically confirmed osteo-arthritis at Royal Melbourne Hospital out-patients clinic were recruited to a double-blind trial comparing 6 mg of boron per day taken orally as two tablets, each containing 25 mg borax (sodium tetraborate decahydrate) to placebo (66% dextrose, 33% dicalcium phosphate, 1% magnesium stearate). All patients gave written consent to participate and the trial was approved by the Royal Melbourne Hospital Ethics Committee.

Patients were excluded from the trial if they were over 75 years of age, had more than 10 years of arthritis or if they had cardiac or renal disease. The patients were assessed three times: prior to taking the tablets, after three weeks on the tablets and after eight weeks on the tablets.

At the initial visit, the patient was asked to rank all the arthritic problem sites in decreasing order of severity and to indicate for each site whether the problems were slight, moderate or severe. At each of the first two visits, the patient was given one bottle of tablets (either borax or placebo as randomized) and two bottles of paracetamol. The patient was requested to use the paracetamol in preference to other analgesics for pain relief.

At three weeks and eight weeks the patient was queried in respect of each of the sites noted at the first visit, and asked to grade the current condition using the following scales:

Completely cured (i.e. pain-free and no restriction of movement);
Much better but not completely cured;
Only slightly better;
No different;
Slightly worse;

Far worse.
The patient was asked whether there were any other sites causing problems which were not noted at the previous visit(s). The relevant details of such sites were recorded. The patient was also asked to give full details of the quantities of palliatives in the intervening three-or five-week period. These quantities, and also patient compliance, were verified by taking counts of the tablets returned. Other relevant data recorded at each visit for each site included whether there was pain on passive movement. Overall assessments as to whether there was any improvement were obtained from both doctor and patient at three weeks and at five weeks.

Ancillary clinical, haematological and biochemical data recorded at each visit comprised weight, pulse, blood pressure and temperature; white blood cell count (WCC), haemoglobin, polymorphs, lymphocytes, platelets, erythrocyte sedimentation rate (ESR), alkaline phosphatase (AP), AST, ALT, Gamma GT, bilirubin, albumin, sodium, potassium, bicarbonate, urea and creatinine. Abnormalities checked for included FBA film abnormalities, mental impairment and inflammation or desquamation of the skin--this latter being a documented effect of acute boron administration [5].

STATISTICAL ANALYSIS

The results were analysed on the Melbourne University VAX computer network using the SPSSX package [6]. Two-way contingency tables were assessed using Fisher's exact test and the goodness of $X^{2, sub 1}$, test. Differences in ratings were assessed using Kendall's rank correlation coefficient. The ancillary clinical, haematological and biochemical data were first examined for normality and then transformed where necessary, a log transformation being required for Gamma GT. The possible effect of boron was then assessed by a regression approach in which possible baseline differences in subjects were taken into account.

RESULTS

Comparison of Treatment Arms

There were three men [1B, 2P] . 2P] means one randomized to boron and two randomized to placebo) and 17 women [9B, 8P]. Their mean age was 64.5 years (range 50-75) and their mean duration of arthritis was 6.3 years (range 3-10). The patients had a total of 93 arthritic joints of which 32 were slightly affected, 45 moderately affected and 16 severely affected. In the two weeks prior to the first visit they took an average of 1.3 palliatives per day (range 0-6). A comparison of the mean data between the two treatment arms is set out in Table 1, the severity being measured on a scale of one (slight) to three (severe). There were no significant differences.

The affected joints comprised: 7 necks, 7 backs, 5 shoulders, I elbow, 12 wrists, 2 hands, 3 knuckles, 13 fingers, 4 hips, 25 knees, 1 ankle, 3 feet, 10 toes. There was no significant locational difference between the two arms, nor was there any significant difference in average severity at the different locations. Pain on passive movement was present at the first visit in 56 (60%) of the affected joints as was swelling, warmth or deformity. Restricted movement was present in 62 (67%).

Two patients [1B, 1P] dropped out of the trial in the three weeks after Visit 1; one (P) probably through lack of response, the other (B) because of intercurrent medical problems. While neither patient had improved on treatment; neither had significantly worsened either. Of the remaining 18 patients [9B, 9P], six [4B, 2P] claimed to have improved while 12 [5B, 7P] claimed to have either worsened or stayed the same. A comparison of the mean data between treatment arms at Visit 2 is set out in Table 2. The condition scale is as set out in the materials and methods section; 1 equates to completely cured; 6 equates to far worse. Once again there were no significant differences.

A further three patients [2B, 1 P] dropped out of the trial in the five weeks after Visit 2; all apparently due to significant deterioration in condition. Of the remaining 15 patients [7B, 8P] six [5B, 1P] claimed to have improved while nine [2B, 7P] claimed to have either worsened or stayed the same. This result in favour of boron was significant ($p < 0.05$, Fisher's exact test) and was confirmed by the doctor who made the identical assessment. The full comparison of the mean data between treatment arms at Visit 3 is set out in Table 3. There was a significantly greater improvement in the condition of all joints on boron than on placebo (Kendall's Tau = 0.34, $p < 0.01$) and there was also significantly less pain on passive movement on boron ($X^{2, sub 1}$ 2, $p < 0.00l$).

Because dropouts were excluded from the Visit 3 analysis in the preceding paragraph, the results undoubtedly overstate the advantage in the boron arm of the trial. When the data from all patients were taken into account, the patients in the boron arm of the trial still did better than those in the placebo arm but the significance is at best marginal. Of the original 10 patients on boron, five improved and five did not, while of the original 10 patients on placebo only one improved (X2=3 8, NS). The average condition of all joints for patients on their last visit was 3.3 for those on boron and 4.0 for those on placebo (Kendall's tau = 0. 26, $p < 0.05$). The average condition for the worst affected joint was 3.9 for those on boron and 4.8 for those on placebo (Kendall's Tau = 0.28, NS).

Other Factors Possibly Affecting Outcome

There was no difference in any of the outcome variables by sex. Older people tended to do slightly worse although not significantly so ($r = 0.30$, NS) as did those who had had arthritis for longer ($r = 0.10$, NS). Improvement was not noticeably more common at particular sites than at others but joints more severely affected at the first visit did noticeably worse than those less affected at the first visit (Kendall's Tau = 0. 18, $p < 0.O5$).

Possible Side Effects

No side effects were observed. The overall means of the ancillary clinical, haematological and biochemical data are set out in Table 4, together with the means for patients when on boron or alternatively when either at the first visit or on placebo. The only result which was significantly different for boron was weight F[sub 1, 31 = 5.3, $p < 0.05$) there being an apparent loss of weight of 0.34 kg for patients when on boron. Subsequent investigation, however, showed that this difference was very largely caused by a drop in weight of over 2 kg over the eight weeks by one woman who was later found to have Hodgkin's lymphoma.

DISCUSSION

There are many grounds on which the results of this trial could be questioned. These include the very small number of patients, the high proportion of dropouts (25%), the low response rate of the placebo patients (10% as against an anticipated rate of 30%) and their slightly worse initial condition.

Counter-arguments could, of course, be strongly mounted against all of these. It was a double-blind randomized trial and there were no departures from protocol. Statistical significance takes account of small numbers. Dropouts were also taken into account in the analysis. In hindsight, a placebo response rate of 30% was probably over optimistic and a response rate of 10% would have been more realistic. The overall group of patients were probably worse than average. Certainly many were on previous therapy which they stopped before commencing the trial. The differences in initial conditions between the groups were not significant and in any case the analysis was made in terms of improvements and not in terms of final conditions.

Such arguments and counter arguments are probably futile. This study was not intended to give a definitive result either in favour or against boron. It was intended as a pilot study. In that respect the result is clear. Further research on the possible role of boron in the treatment of arthritis seems to be justified.

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TABLE 1. Comparison of mean presentation data between the treatment arms

Variable	Boron arm	Placebo arm	Total
Age	64.9	64.0	64.5
Years of arthritis	6.3	6.4	6.4
Number of joints affected	4.2	5.1	4.7
Severity of joints affected	1.7	1.9	1.8
With pain on movement (%)	50.0	69.0	60.0
With swelling, etc. (%)	50.0	69.0	60.0
With restricted movement (%)	64.0	69.0	67.0
Palliatives per day prior to Visit 1	0.9	1.8	1.3

TABLE 2. Comparison of the mean Visit 2 data between the treatment arms

Variable	Boron arm	Placebo arm	Total
Number of joints affected	4.2	5.7	4.9

Condition of worst joint	4.1	4.6	4.3
Condition of all joints	3.7	3.5	3.6
With pain on movement (%)	45.0	65.0	56.0
With swelling, etc. (%)	55.0	61.0	58.0
With restricted movement (%)	61.0	65.0	63.0
Palliatives per day between Visits 1 and 2	2.3	2.7	2.5

TABLE 3. Comparison of the mean Visit 3 data between the treatment arms

Variable	Boron arm	Placebo arm	Total
Number of joints affected	4.0	5.8	4.9
Condition of worst joint	3.3	4.6	4.1
Condition of all joints	3.0	3.9	3.6
With pain on movement (%)	27.0	70.0	54.0
With swelling, etc. (%)	46.0	57.0	53.0
With restricted movement (%)	54.0	70.0	64.0
Palliatives per day between Visits 1 and 2	0.8	2.5	1.8

TABLE 4. Means of the ancillary monitoring data for patients when on boron and when not on boron

Parameter	Mean on boron	Mean not on boron	Overall mean
Weight	62.8	71.3	68.9
Pulse	73.9	73.9	73.9
Blood pressure	138/81	147/80	144/80
Temperature	36.9	36.9	36.9
WCC	7.3	7.5	7.5
Hb	13.1	13.7	13.5
Polymorphs	4.2	4.6	4.5
Lymphocytes	2.2	2.0	2.0
Platelets	328.1	301.2	309.0
ESR	19.3	21.9	21.2
AP	78.7	84.3	82.6
AST	23.7	22.9	23.1
ALT	20.9	29.9	27.2
GamaGT	20.7	26.3	24.7
Bilirubin	7.0	6.7	6.8
Albumin	42.8	42.0	42.2
Na	139.9	140.5	140.3
K	4.4	4.2	4.3

Bicarbonate	26.7	27.0	26.9
CI	102.7	104.0	103.6
Urea	6.7	6.9	6.8
Creatinine	0.09	0.09	0.09

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